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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CLOW, LORI A	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 10/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,648	PRESTEGARD ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2004 and 09 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-16,19 and 20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-16,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' response, filed 27 July 2004, and Supplemental Response, filed 9 August 2004, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-4, 6-16, and 19-20 are currently pending. Claims 5, 17, 18, and 21-25 have been cancelled.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See, for example, page 26, line 5 and line 21. Applicant has attempted to correct this by an amendment to the specification submitted on 27 July 2004 and 9 August 2004. However, the text still contains embedded hyperlinks. See page 26 (http:// tesla.ccrc.uga.edu). Correction is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 19-20 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 19 still recite "a method for improving the binding affinity of a ligand for a biological target". However, there is no step of improving the binding affinity in the claim. The final step is drawn to selecting or preparing a compound. Clarification is requested.

Claim 20, step (c) still recites "substantially". It is unclear as to the metes and bounds of the word "substantially". Does this mean that the orientation is almost in the relative position or exactly in the relative position? Applicant states that it means both "almost in the relative position" and "exactly in the relative position". However, what are the metes and bounds of being "almost" in the relative position? Does this mean within a certain distance, for example no more than within 5 angstroms? Clarification is requested.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16 and 19-20 are rejected under 35 U.S.C. 103(a) as being obvious over Johnson et al. (Journal of Molecular Biology (1999) Vol. 287, pages 609-625; PTO Form 1449 Reference AJ), in view of Bolon et al. (Journal of Molecular Biology (1999) Vol. 293, pages 107-115; PTO Form 1449 Reference AG).

The instant invention is drawn to a method for improving the binding affinity of a ligand for a biological target comprising preparing a first NMR spectra of a complex comprising a biological target and a parmagnetically labeled derivative, preparing a second NMR spectra of a second complex comprising a biological target and a second ligand, analyzing spectra to determine if the second ligand binds to the target in the parmagnetic zone of the paramagnetically labeled derivative.

Johnson et al. teach a method of using NMR spectroscopy (HSQC spectra) to provide structural understanding of the binding properties of CBD_{N1} and CBD_{N2} (N-terminal cellulose binding domains from *Cellulomonas fimi* cellulase CenC). The structures of CBD_{N1} and CBD_{N2}

were calculated using NMR data collected for these protein domains in the presence of concentrations of cellotetaose or cellopentaose, respectively (page 610, column 2). Derivatives of cellotriose and cellotetraose were prepared with 2,2,6,6-tetramethylpiperidine-1-oxy-4-ol (TEMPO) spin-label covalently attached to the reducing end of the sugar. TEMPO is a paramagnetic relaxation probe. The labeled sugars can be used to obtain long range distance information about the CBD-cellooligosaccharide complexes (page 610, column 2). It was determined that the modified sugars bind to CBD_{N1} and CBD_{N2} in both possible orientations. The interactions of the TEMPO-labeled cellooligosaccharides with CBD_{N1} and CBD_{N2} were analyzed by monitoring the $^{1}H^{5}$ and ^{15}N chemical shifts of the proteins upon titration with these sugars. The spectral changes were similar to those observed for the unlabelled cellooligosaccharides (page 611, column2). Perturbation effects were also studied (beginning page 612, column 1-page 613, column 1). Inspection of the HSQC spectra of the complexes provided the binding orientation of the sugars. Three-dimensional orientations were also deduced as seen in Figure 8. Multiple binding orientations were uncovered by studying the effects of the TEMPO-Glc_3 and TEMPO-Glc_4 on relaxation properties of CBD_{N1} and CBD_{N2}. Given the TEMPO-labeled sugars and the corresponding unmodified cellooligosaccharides bind the CenC CBDs with similar affinities and produce similar chemical shift perturbations, the conclusion was that Glc_3 and Glc_4 are bound in multiple orientations (see discussion) (binding elucidation).

Johnson et al. do not teach deducing a relative three-dimensional orientation of the first and second ligands when bound to the biological target; deducing the distance of separation of the first and second ligands; and selecting or preparing a compound that contains the first and

second ligands in relative orientation and distance. Johnson et al also do not teach field ordered states, as in claims 7-9. However, Bolon et al. do teach the method of determining ligand geometry in protein binding that relies on orientational constraints derived from residual dipolar couplings (the method used to determine 3-D orientation) observed in NMR spectra or partially ordered macromolecular complexes (page 107, column 1). The approach is based upon the observation of residual dipolar coupling of directly bonded ^{1}H-^{13}C pairs in α-methyl mannoside (AMM) when mannoside is bound to MBP in a field-oriented aqueous liquid crystal (page 109, column 1). Bolon et al. also teach "deducing orientation by producing field ordered states, including inherent orientation due to the large anisotropies in the magnetic susceptibilities of some molecules orientation due to the interaction of molecules with lipid bicelles that form in field-oriented liquid crystals and interaction with filamentous bacteriophage that also form field-oriented liquid crystals (page 108, column 2)".

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used three-dimensional determination and distance orientation using field ordered states of Bolon et al. in the method of Johnson et al., as motivated by Johnson et al. at page 621, column 1, which states: "further structural studies [...] are necessary to understand the mechanisms by which this and other cellulolytic enzymes function in the efficient degradation of biomass". Bolon et al. further state that "transfer NOE studies (such as those of Johnson et al.) while giving sound information on ligand geometry, suffer from a lack of information on the nature of the ligand protein contacts (page 107, column 2) [...]. In these difficult cases, residual dipolar data can offer a valuable alternative, where data can in principle constrain both bound ligand geometry and ligand orientation relative to the protein binding site (page 108, column 2)".

Response to Applicant's Arguments

35 USC 112, 2nd Paragraph

Applicant argues that the amendments to the claims have overcome the outstanding rejections under 35 USC 112, 2nd paragraph. However, for the reasons stated above, the rejections have not been overcome.

35 USC 102

Applicant argues that the Johnson et al. reference does not teach deducing a relative three-dimensional orientation of the first and second ligands when bound to the biological target; deducing a distance of separation of the first and second ligands when bound to the biological target; and selecting or preparing a compound that contains the first and second ligands substantially in the relative orientation and distance, as recited in the pending claims. In view of the new grounds of rejection which was necessitated by amendment, this argument is moot (see rejection above).

35 USC 103

Applicant argues that because Johnson et al. do not teach the limitations recited above, Fischer et al. does not overcome the deficiency present. This argument is moot in view of the new grounds of rejection set forth above.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center Number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of

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MARJORIE MORAN
PATENT EXAMINER

10/21/04

October 20, 2004
Lori A. Clow, Ph.D.
Art Unit 1631